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Autophagy in renal distal tubules attenuates tubulointerstitial fibrosis through regulating TGF- β and IL1- β after unilateral ureteral obstruction

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Objectives: Renal fibrosis is the final common pathway of various renal injuries and it leads to chronic kidney disease. Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death and proliferation. Cellular response during unilateral ureteral obstruction (UUO) is tubular segment specific. Thus the role of autophagy on renal tubulointerstitial fibrosis (TIF) after UUO may be different according to segment of nephron. The role of autophagy during UUO remains unclear especially in distal tubules. In this study, we investigated the role of autophagy in distal tubules on renal TIF using conditional knockout mice in which Atg7 was genetically ablated specifically in distal tubular epithelial cell (TEC).

Methods: To examine whether autophagy is induced in renal distal tubular cells after UUO, we used green fluorescent protein (GFP)-LC3 transgenic mice. To investigate the role of autophagy in distal tubules on renal TIF, Atg7^{flox/flox} mice were crossed with Ksp-Cre mice to generate distal tubule-specific Atg7 knockout mice (Atg7^{flox/flox};Ksp-Cre mice). Atg7^{flox/flox} littermates served as controls. UUO was performed.

Results: In GFP-LC3 transgenic mice, GFP-LC3 puncta was highly expressed in Tamm-Horsfall protein (THP)-positive cells of the obstructed kidneys after UUO. Genetic deletion of Atg7 specifically in distal TEC enhanced the expression of transforming growth factor (TGF)- β and increased renal tubulointerstitial fibrosis and epithelial-mesenchymal transition-like phenotype change after UUO. Distal tubule-specific autophagy-deficient mice increased the accumulation of SQSTM1/p62-positive aggregates in the obstructed kidney and resulted in increased expression of interleukin (IL) 1- β and caspase-1. Distal TEC-specific Atg7 deletion damaged mitochondria and enhanced apoptosis of TECs after UUO.

Conclusions: In summary, our data showed that autophagy in distal TEC plays a protective role in development of renal tubulointerstitial fibrosis through regulating the expression of TGF- β and IL1- β after UUO.